

The Examiner maintained the rejection of claims 1-23 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,242,246 (Gold et al.). Applicants respectfully traverse this rejection.

The Examiner rejected claims 1-23, 28-35, 42-64, and 69-72 under 35 U.S.C. § 112, first paragraph as not being enabled. Applicants respectfully traverse this rejection.

Rejection under 35 U.S.C. § 112 Second Paragraph

The Examiner rejected claims 1-23 under 35 U.S.C. § 112, second paragraph as being indefinite. Specifically, the Examiner asserts that the instant claims recite a phrase "electromagnetic signal characteristic of the biological activity" which is confusing and unclear as to what the phrase refers to because any light or fluorescence spectrum releases electromagnetic signal and it is not clear how a signal can be characteristic of biological activity, an absorbance reading of a biological or a chemical reaction by spectrophotometer could be an electromagnetic signal.

Although Applicants think that they have explained the meaning of this phrase, Applicants offer the following as further explanation. The Applicant specified in the description, page 5 lines 11 to 30, the meaning of the phrase "electromagnetic signal characteristic of a biological activity".

Furthermore, by "electromagnetic signal characteristic of the biological activity" of an element is understood the electromagnetic signal picked up from a biologically active element such as a substance, a cell or a micro-organism, etc., or from a material containing this element such as a purified preparation, a biological sample, an organ or a living being, as has been described in International Application WO 94/17406 in the name of J. BENVENISTE. By "electromagnetic signal characteristic of the biological activity" of an element is also understood the signals derived from a signal as defined above by signal digitization and/or processing. Furthermore, in this expression, the term "characteristic" is used in the sense that the picked up electromagnetic signal contains information characterizing the fact that the material from which this signal is picked up shows the biological activity in question. The electromagnetic signal picked up from a material containing a plurality of biologically active elements shows the biological activity of each of the elements that it contains.

The signal is therefore a signal picked up from an element having biological activity (see "the electromagnetic signal picked up from a biologically active element"). The Applicant showed how such a signal could be picked up, specifically the Applicant

cited to International Application WO 94/17406. This application, filed before the filing of the present application, describes a method and a device for picking up such a signal. The Applicant also explained the word "characteristic" in the phrase "electromagnetic signal characteristic of a biological activity". It means that the signal contains information characterizing the fact that the initial element has a determined biological activity.

It is the Applicants understanding that the Examiner does not accept these explanations for three reasons.

First, " It is unclear how a signal can be characteristic of biological activity since a signal intensity is measured as proportional to biological activity in any biochemistry reactions". The electromagnetic signal that is picked up has characteristics which are not limited to measurements of intensity. The form of the signal, its spectrum, its phases, etc. may amount to the signature of biological activity. The Applicants have found that it is possible to obtain (from an element having biological activity) an electromagnetic signal having properties that can amplify the formation of a ligand-receptor complex using this element. It is not necessary for Applicants to describe the physical characteristics of the signal, which quite complex. On the other hand, Applicants are bound to explain how this signal can be produced and recorded in a form enabling persons skilled in the art to produce and record this same signal. Applicants have carried out this task. In order to more fully clarify the invention, Applicants have amended claim 1 by incorporating the recitations of claim 32 to explain the method used to produce characteristic signals.

Second, " It is not clear whether the electromagnetic signal as recited in the specification does or does not correlate with the biological activity". Applicants are unclear what the Examiner means by this, however, Applicants offer the following. According to the invention, a signal derived from a substance having a determined activity is picked up, a substance of the same type as the determined substance is contacted with another substance with which a ligand-receptor complex can be formed, said signal is applied to one of the elements of the ligand-receptor pair or to the ligand pair, and it is found that the reaction of ligand-receptor complex formation is amplified by the action of the signal. Applicants respectfully assert that the physicochemical mechanisms according to which the signal is correlated with the biological activity of the original substance do not need to be described, even if known. Provided that the

Applicants have described the method and technical means with which it is possible to obtain the observed effects, such entitles Applicants to obtain a patent whose purpose is the industrial application of the observed effects.

Third, " Further it is not clear how the EM signal is considered to characterize the biological activity". In this third comment, the Examiner raises an issue which Applicants respectfully assert does not constitute a criterion for patentability. The specification need not necessarily contain a technical explanation of the physiochemical reasons why the signal is correlated with the biological activity of the original substance.

35 U.S.C. § 102 Rejections

The Examiner rejected claims 1-23, and 28-31 under 35 U.S.C. § 102(a) as being anticipated by Benveniste et al. (FASEB J., March 17, vol. 12(4); pp A412, 1998) ("Benveniste I").

Applicants amended claim 1 by adding the limitations of claim 32. Applicants note that claim 32 was not rejected over Benveniste I by the Examiner. Therefore, Applicants respectfully assert that newly amended claim 1 is not anticipated by Benveniste I.

The Examiner inaccurately summarizes Benveniste I by indicating that its teaching is "bringing into contact ligand (agonist) with receptor (target cell)". Benveniste I teaches the application of an electromagnetic signal to a receptor (target cells or organs). The confusion from which the Examiner endeavors to draw advantage is derived from the fact that in the abstract the electromagnetic signals so applied are designated under the name EM "ligands". An electromagnetic signal cannot be confused with a substance able to bind with another substance to form complexes. Moreover, Applicants specified the notion of a ligand :

In what precedes and what follows, by the term "reagent" is denoted any preparation of which the composition is known, which contains the ligand or the receptor in an also known quantity and presents itself either in a dry form such as a lyophilisate to be reconstituted in a solvent, or in a liquid form such a solution or a suspension, the ligand and the receptor being able to be fixed on a solid phase (particles or beads of latex, glass or polystyrene etc.).

Applicants respectfully assert that there is no possible ambiguity: a "ligand" as used in Applicants' invention is a material substance, it is not an electromagnetic wave.

Furthermore, in the cited document the teaching of a process for amplifying the reaction

between a ligand and a receptor to form complexes is not found. Therefore the cited document does not allude to the problem solved by Applicants' invention.

In the Examiner's reply to Applicants' arguments, the Examiner asserts that the prior art teaches each of the limitations of former claim 1. To demonstrate her view, the Examiner asserts that the claim also covers the case in which the electromagnetic signal (EM) is applied after formation of the ligand-receptor complex. This is inaccurate, the claim specifies that the electromagnetic signal (EM) is applied before "said ligand and said receptor are brought into contact" or simultaneously, that is to say before the complex formation reaction occurs. It is not possible to confuse the contacting phase and the complex formation phase. The claim specifies that the purpose of the process is to amplify the reaction between a ligand and a receptor by applying an electromagnetic signal (EM), it cannot be said therefore that the claim could be taken to mean when the electromagnetic signal (EM) is applied after formation of the complex. Applicants respectfully assert that such an interpretation of the claim is not consistent with the language used.

The Examiner adds a further argument which Applicants take exception to. According to the Examiner, Benveniste I teaches that an electromagnetic field can activate biological systems. It is therefore concluded by the Examiner that such activation can only result from amplification of a physicochemical reaction between a ligand and a receptor. It is inaccurately and with no substantiation that the Examiner considers that the activation of a biological system can only result from amplification of a physicochemical reaction between a ligand and a receptor. The activation of a biological system may result from the application of purely electrical phenomena. Applicants respectfully assert that the Examiner incorrectly utilized hindsight reconstruction.

The Examiner rejected claims 1-23, 28-35, and 42-64 under 35 U.S.C. § 102(b) as being anticipated by Benveniste et al. (J. Allergy Clin Immunol., vol. 99(1), part 2, pp S175, 1997) ("Benveniste II").

The new limitations added to claim 1 specify the method according to which a signal that is characteristic of biological or chemical activity or characteristic of the biological or chemical behavior of a substance can be produced. The method comprises the two following steps:

- "placing said substance in a zone subjected to an excitation field of an electrical, magnetic or electromagnetic type, . . . ; and

- converting the fields resulting from the interaction of the interaction of said excitation field and substance into signals by means of a transducer or acquisition sensor receiving said resulting field, ...”

Benveniste II does not teach applying an excitation electromagnetic field prior to recording the signal produced by ovalbumine. Benveniste II teaches the direct recording of the signal produced by Ovalbumine with no prior excitation by an electromagnetic field. The inventors, including Jacques Benveniste, were unaware at the time Benveniste II was published that prior application of an excitation field facilitated the production of a signal forming the signature of a substance.

These additional explanations clearly demonstrate that the prior art does not teach the limitations of new claim 1, in particular those resulting from the incorporation of the technical characteristics of ex-claim 32.

The Examiner maintained the rejection of claims 1-23 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,653,939 (Hollis et al.). Applicants respectfully traverse this rejection. Applicants amended claim 1 by adding the limitations of claim 32. Applicants note that claim 32 was not rejected over Hollis et al. by the Examiner. Therefore, Applicants respectfully assert that newly amended claim 1 and the dependent claims are not anticipated by Hollis et al..

The Examiner maintained the rejection of claims 1-23 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,242,246 (Gold et al.). Applicants respectfully traverse this rejection. Applicants amended claim 1 by adding the limitations of claim 32. Applicants note that claim 32 was not rejected over Gold et al. by the Examiner. Therefore, Applicants respectfully assert that newly amended claim 1 and the dependent claims are not anticipated by Gold et al..

35 U.S.C. § 112, First Paragraph Rejection

The Examiner rejected claims 1-23, 28-35, 42-64, and 69-72 under 35 U.S.C. § 112, first paragraph as not being enabled.

The Examiner asserts that the claims are drawn to a method of amplifying a reaction between a ligand and a receptor of a ligand-receptor pair comprising applying electromagnetic (EM) signal characteristic of biological activity to at least one of the said pair and amplifying or increasing the reaction process of formation of the said ligand-receptor complex. The Examiner also asserts that the invention is a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology".

Applicants respectfully assert that the invention does not concern a method for synthesizing a determined chemical molecule or one belonging in general to a chemical family. The invention concerns a general physicochemical process which occurs during the formation of ligand-receptor complexes irrespective of the nature of the ligand or receptor or of the formed complex. The process of the invention is of the same nature as the process consisting of heating or agitating reagents.

Persons skilled in the art know how to proceed to agitate reagents of different kinds when given the teaching of applying an agitation phase.

In the case at hand:

- picking up a signal under conditions that are the subject of newly amended claim 1, such as supported by the description, then,
- applying this signal to a ligand-receptor pair
is an operation that is as easy to implement as the operation consisting of heating reagents.

The Examiner therefore unduly claims that the invention comes under the class of "unpredictable arts such as chemistry and biology".

The Examiner also asserts that the claims encompass a method of increasing the formation of a ligand-receptor complex by applying electromagnetic (EM) signals characteristic of biological activity to, said pair or at least to one member of the pair; that no specific type of electromagnetic signal characteristic of biological activity is recited in the specification and thus the claims encompass all electromagnetic, signal generating sources such as UV, infra-red, x-rays and visible wave length rays to apply to the said pair. The Examiner also asserts that no specific EM signal is recited that is characteristic of biological activity. EM signals picked up by the ligand-receptor complex does not reasonably provide enablement for biological activity associated with ligand-receptor complex formation when EM is applied.

By combining the technical characteristics of previously pending claim 32 with new claim 1, Applicants have explained in a very clear manner how to produce the electromagnetic signal to be applied to a ligand-receptor pair. It suffices to pick up the field resulting from the interaction of the ligand and/or receptor with an excitation field having frequencies lying between 20Hz and 20 000 Hz.

Applicants provided a teaching that is richer than required by the Examiner since it provides the technical means to obtain such a signal. Under these conditions, it cannot be held against the Applicant that no definition is given of the signal to be applied.

The Examiner also asserts that the quantitation of experimentation in this area is extremely large since amplification of EM signals characteristic of biological activity would require, initially, *in vitro* to demonstrate proof of the principle. Put in other words, prior to any result intervention, it would be necessary to create a biological molecule which is active as recited in the specification which could be activated or show increase in activity or the effect of EM signal on the active biological molecule, then show this effect would have some potential effect of in a reaction process with these active biological molecules, a series of showings not present in the specification.

Applicants respectfully assert that they have provided a simple method to implement, requiring a few days at the most after an initial learning phase. The results (amplification of the formation of a complex) can be assessed by means of usual physico-chemical analysis methods.

Persons skilled in the art are therefore able to evaluate rapidly whether the method claimed in the instant application has substantial effects on ligand-receptor pairs whose formation it is desired to amplify.

Applicants cannot be compelled to test every imaginable ligand-receptor complex. The invention relates to an amplifying method (an operating process). It does not relate to a family of particular biological compounds. The applicant is not bound, therefore, to test all complexes belonging to this family provided they have shown in some examples (as is the case in the description) that the effects produced by the claimed operating process are indeed those that are claimed. It is for persons skilled in the art to use the claimed method for the ligand-receptor pair of their choice.

The Examiner asserts that the art teaches that the field of biology related to EM is one of the most unpredictable areas of human endeavor for which patents are sought. The Examiner

also asserts that the prior art also supports the unpredictable nature of the art associated with biological molecules. Thus prior art not only fails to, support the efficacy of the invention, but in fact, supports the unpredictability.

Applicants respectfully assert that an applicant who files a patent application concerning industrial applications of a reproducible physicochemical phenomenon is not bound to explain the theoretical foundations of the phenomena observed. He is not bound to give a detailed explanation of the mechanisms which could be used to calculate and to predict beforehand the quantitative magnitude of the expected effects.

The experimental method, the protocol described in the patent application is the most appropriate manner to quantitatively evaluate the effects arising from implementation of the claimed method. The prior art confirms that in many technical sectors, it is necessary to conduct tests (on a reduced scale) before industrial implementation of operating processes whose mathematical modeling proves to be complex and uncertain. But this does not mean that inventions made in these industrial sectors are excluded from the field of patentability.

The Examiner also asserts that the specification has no working examples to show application of EM amplifies biological activity of ligand-receptor complex.

Applicants respectfully assert that this is inaccurate. Moreover, this is implicitly admitted by the Examiner since in the following paragraph of the official letter she acknowledges that the description "teaches the identification of E.coli antigen-antibody complex formation".

Such application is sufficient in itself to justify the industrial nature and practical interest of the invention. It is surprising to ascertain that an Examiner considers that an operating process with which it is possible to identify bacteria or pathogenic viruses, streptococcus and HIV viruses in particular, are of secondary interest or even fully eclipses the matter. Applicants are able to produce experimental results, obtained since the application was filed, establishing such facts.

The Examiner also asserts that the specification solely teaches the increase in the indexes of complex formation when the EM signal is applied, and provides absolutely no teaching or suggestion regarding any characterization of biological activity based on EM signals picked up the complex, nor are any amplification of EM signals in the said reaction which are picked up by unreacted biological molecules (ligand alone or receptor alone) of the pair or other biological molecules of the reaction. The Examiner also asserts that no specific teachings regarding the use

of any ligand-receptor pair in characterizing biological activity except the identification of E.coli antigen-antibody complex formation.

The applicant notes that the examiner acknowledges that: "The specification teaches the increases in the indexes of complex formation when the EM signal is applied". As to the remainder, Applicants do not understand the sentence written by the Examiner. It would appear that the Examiner confuses between amplification of the formation of the ligand-receptor complex and amplification of the EM signal. These two notions are extraneous and cannot be easily correlated.

The Examiner notes that the skill in the art is high. It is true that persons skilled in the art must be competent in biology, the physics of electromagnetic fields, microelectronics and data processing. But this is the competence of persons skilled in the art concerned by the cited prior art (see especially the Hollis and Gold patents).

Such level of competence cannot be qualified as "high": for those scientists and engineers who innovate in this sector of activity, it is trivial. Persons skilled in the art in the sector concerned have every skill to implement the invention.

In summary, Applicants submit that the specification does enable one of skill in the art to make and use the invention. Applicants therefore respectfully request that this rejection be withdrawn.

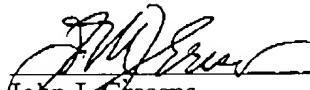
Conclusion

In view of the amendments and comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested.



Date: 3/10/03

Respectfully submitted,
MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
612.332.5300


John J. Gresens
Reg. No. 33,112
JJG:AMN

Marked up version of ClaimsIn the Claims

Please cancel claim 32 without prejudice. Please amend claim 1 as follows.

1. (Amended) A process for amplifying a reaction between a ligand and a receptor of a ligand-receptor pair comprising:

a.) producing or acquiring, from said ligand and/or receptor signals that are characteristic of the biological or chemical activity or the biological or chemical behavior of said ligand and/or receptor said signals being produced or acquired according to a method comprising:

i.) placing said ligand and/or receptor in a zone subjected to an excitation field of an electrical, magnetic or electromagnetic type, wherein said excitation field is produced by an excitation signal having a frequency between about 20 Hz and about 20,000 Hz; and

ii.) converting the fields resulting from the interactions of said excitation field and said ligand and/or receptor into signals by means of a first transducer or acquisition sensor receiving said resulting fields, wherein said signals are characteristic of the biological or chemical activity or behavior of said ligand and/or receptor

b.) bringing said ligand and said receptor of said ligand-receptor pair into contact in conditions suitable to allow their reaction; and

c.) applying [at least one] said electromagnetic signal characteristic of the biological activity of at least one of said ligand or said receptor to at least one of said ligand or receptor, wherein said electromagnetic signal can be applied prior to, simultaneous with, or subsequent to said ligand and said receptor being brought into contact,

wherein said process amplifies the reaction at least in part by increasing the binding affinity properties of at least one of said two elements.